(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 September 2006 (21.09.2006)

PCT

(10) International Publication Number
WO 2006/097766 A1

(51) International Patent Classification:
A61K 31/10 (2006.01) *A61K 31/415* (2006.01)
A61K 31/44 (2006.01) *A61K 31/4164* (2006.01)
C07C 317/14 (2006.01) *A61K 31/4184* (2006.01)
C07D 213/71 (2006.01) *A61K 31/4196* (2006.01)
A61P 25/00 (2006.01) *A61K 31/426* (2006.01)
A61K 31/166 (2006.01) *C07D 213/80* (2006.01)
A61K 31/18 (2006.01) *C07D 213/82* (2006.01)
A61K 31/277 (2006.01)

(21) International Application Number:
PCT/GB2006/050048

(22) International Filing Date: 8 March 2006 (08.03.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0505437.4 17 March 2005 (17.03.2005) GB

(71) Applicant *(for all designated States except US)*: **MERCK SHARP & DOHME LIMITED** [GB/GB]; Hertford Road, Hoddesdon, Hertfordshire EN11 9BU (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **CHAMBERS, Mark, Stuart** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **GILLIGAN, Myra** [IE/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **HUMPHRIES, Alexander, Charles** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB). **MERCHANT, Kevin, John** [GB/GB]; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

(74) Agent: **BUCHAN, Gavin**; Terlings Park, Eastwick Road, Harlow, Essex CM20 2QR (GB).

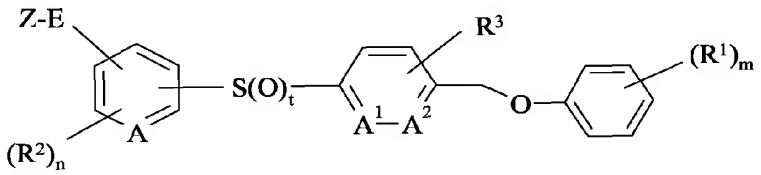
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) **Title:** ARYLSULFONYL BENZYL ETHERS AS 5-HT_{2A} ANTAGONISTS



(I)

(57) **Abstract:** Compounds of formula (I) are potent and selective antagonists of the 5-HT_{2A} receptor, and hence are useful in treatment of various CNS disorders.

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ARYLSULFONYL BENZYL ETHERS AS 5-HT_{2A} ANTAGONISTS

The present invention relates to a class of sulphonyl derivatives which act on serotonin receptors (also known as 5-hydroxytryptamine or 5-HT receptors). More particularly, the invention concerns a class of arylsulphonylbenzyl ethers. These compounds are potent and selective antagonists of the human 5-HT_{2A} receptor and are therefore useful as pharmaceutical agents, especially in the treatment and/or prevention of adverse conditions of the central nervous system, including sleep disorders such as insomnia, psychotic disorders such as schizophrenia and psychiatric disorders such as anxiety.

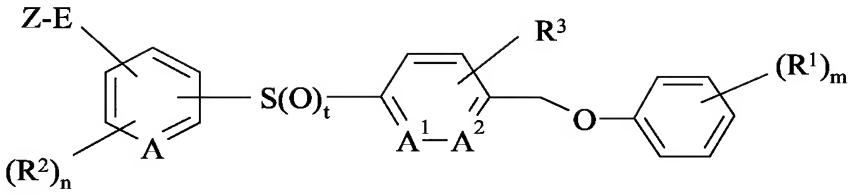
Compounds of the invention typically display more effective binding to the human 5-HT_{2A} receptor than to other human receptors such as D_2, $5HT_{2C}$ and IKr receptors. They can therefore be expected to manifest fewer side-effects than compounds which do not discriminate in their binding affinity between such receptors. In particular these compounds have lower effects on the IKr receptors and there is a separation of the desired effect from side effects such as cardiac effects.

By virtue of their potent human 5-HT_{2A} receptor antagonist activity, the compounds of the present invention are effective in the treatment of neurological conditions including sleep disorders such as insomnia, psychotic disorders such as schizophrenia, and also depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, eating disorders such as anorexia nervosa, and dependency or acute toxicity associated with narcotic agents such as LSD or MDMA; and moreover are beneficial in controlling the extrapyramidal symptoms associated with the administration of neuroleptic agents. They are also effective in the lowering of intraocular pressure and hence in treating glaucoma, and may also be effective in treating menopausal symptoms, in particular hot flushes (see Waldinger et al, *Maturitas*, 2000, **36**, 165-8).

Various classes of compounds containing *inter alia* a sulphonyl moiety are described in WO 2005/047246, WO 2005/047247, WO 03/099786, WO 2004/101518, WO 01/74797, WO 00/43362, WO 96/35666, EP-A-0261688, EP-0304888, and US Patents 4,218,455 and 4,128,552, DE-A-3901735 and Fletcher *et al, J. Med. Chem.*, 2002, **45**, 492-503. None of these publications, however, discloses or suggests the particular class of compounds provided by the present invention.

The compounds according to the present invention are potent and selective 5-HT_{2A} receptor antagonists, suitably having a human 5-HT_{2A} receptor binding affinity (K_i) of 100 nM or less, typically of 50 nM or less and preferably of 10 nM or less. The compounds of the invention may possess at least a 10-fold selective affinity, suitably at least a 20-fold selective affinity and preferably at least a 50-fold selective affinity, for the human 5-HT_{2A} receptor relative to the human dopamine D_2 receptor and/or the human IKr and/or 5-HT_{2c} receptors. Preferred compounds show selectivities of at least 100-fold relative to the human 5-HT_{2c} receptor.

According to the invention there is provided a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I:



I

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2 or 3;

n is 0, 1 or 2;

t is 1 or 2;

A represents CH or N;

A^1 and A^2 each represent CH or N but do not both represent N:

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally incorporating an oxygen atom to form an ether linkage;

Z is selected from halogen, CN, nitro, CF_3, OCF_3, $-R^a$, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aCO_2NR^aR^b$, $-NR^aS(O)_tR^a$, $-NR^aSO_2NR^aR^b$, $-COR^a$, $-CO_2R^a$, $-CONR^aR^b$, $-CR^a{=}NOR^b$ or a five- or six-membered heteroaromatic ring optionally bearing up to 2 substituents selected from halogen, CN, CF_3, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, amino, C_{1-6}alkylamino and di(C_{1-6})alkylamino;

or the moiety –E-Z may combine with an adjacent R^2 group as defined below;

R^a and R^b independently represent H or a hydrocarbon group of up to 7 carbon atoms which is optionally substituted with up to 3 fluorine atoms and optionally with Cl, Br, CN, OH, C_{1-4}alkoxy, C_{1-4}alkylthio, amino, C_{1-4}alkylamino or di(C_{1-4})alkylamino; or R^a and R^b, when linked through a nitrogen atom, together represent the residue of a heterocyclic ring of 4, 5 or 6 members, optionally bearing up to 3 substituents selected from halogen, CN, CF_3, oxo, OH, C_{1-4}alkyl and C_{1-4}alkoxy;

each R^1 independently represents halogen, CN, OH, C_{1-4} alkoxy or hydroxymethyl;

each R^2 independently represents halogen, CN, $CONH_2$, C_{1-4}alkyl or C_{1-4}alkoxy; or an R^2 group and the moiety –E-Z when attached to adjacent ring positions may complete a fused imidazole ring;

and R^3 represents H, halogen, CN, CF_3, OR^a, CO_2R^a, $CONR^aR^b$, NR^aR^b or C_{1-4}alkyl which is optionally substituted with halogen, CN, CF_3, OR^a, CO_2R^a, $CONR^aR^b$ or NR^aR^b.

In a particular embodiment of the invention, -E-Z does not combine with an adjacent R^2 group.

Compounds of formula I in which –E-Z is other than H are believed to be novel, and constitute a further aspect of the invention.

Compounds of formula I in which m is 1 or 2 and R^1 represents fluorine are believed to be novel, and constitute a further aspect of the invention.

Where a variable occurs more than once in formula I or in a substituent group thereof, the individual occurrences of that variable are independent of each other, unless otherwise specified.

As used herein, the expression "hydrocarbon group" refers to groups consisting solely of carbon and hydrogen atoms. Such groups may comprise linear, branched or cyclic structures, singly or in any

combination consistent with the indicated maximum number of carbon atoms, and may be saturated or unsaturated, including aromatic when the indicated maximum number of carbon atoms so permits unless otherwise indicated.

As used herein, the expression "C_{1-x}alkyl" where x is an integer greater than 1 refers to straight-chained and branched alkyl groups wherein the number of constituent carbon atoms is in the range 1 to x. Particular alkyl groups are methyl, ethyl, n-propyl, isopropyl and t-butyl. Derived expressions such as "C_{2-6}alkenyl", "hydroxyC_{1-6}alkyl", "heteroarylC_{1-6}alkyl", "C_{2-6}alkynyl" and "C_{1-6}alkoxy" are to be construed in an analogous manner. Most suitably, the number of carbon atoms in such groups is not more than 6.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, of which fluorine and chlorine are preferred and fluorine particularly preferred.

The expression "C_{3-6}cycloalkyl" as used herein refers to nonaromatic monocyclic hydrocarbon ring systems comprising from 3 to 6 ring atoms. Examples include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cyclohexenyl.

For use in medicine, the compounds of formula I may be in the form of pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds of formula I or of their pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, sulphuric acid, methanesulphonic acid, benzenesulphonic acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Alternatively, where the compound of the invention carries an acidic moiety, a pharmaceutically acceptable salt may be formed by neutralisation of said acidic moiety with a suitable base. Examples of pharmaceutically acceptable salts thus formed include alkali metal salts such as sodium or potassium salts; ammonium salts; alkaline earth metal salts such as calcium or magnesium salts; and salts formed with suitable organic bases, such as amine salts (including pyridinium salts) and quaternary ammonium salts.

When the compounds according to the invention have one or more asymmetric centres, they may accordingly exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof in any proportion are encompassed within the scope of the present invention.

In the compounds of formula I, t is 1 or 2. In a preferred embodiment t is 2.

In formula I, A represents CH or N. In a particular embodiment, A represents CH. When A represents N, the moiety S(O)t may be attached at any of the positions of the resulting pyridine ring in Formula I, but attachment at the 2- or 3- position relative to the ring N is preferred, and attachment at the 2-position particularly preferred.

A^1 and A^2 each represents CH or N; but do not both represent N. In a preferred embodiment A^1 and A^2 both represent CH.

Where E represents a straight or branched alkylene chain, this may be, for example, methylene, ethylene, 1-methylethylene, propylene, 2-methylpropylene or butylene. The alkylene chain E may optionally incorporate an oxygen atom, thereby forming an ether linkage such as $-CH_2O-$ or $-CH_2CH_2CH_2O-$. Moreover, E may represent a chemical bond such that the moiety Z is attached directly to the relevant phenyl or pyridyl ring depicted in formula I above.

Preferably, E represents a chemical bond or a methylene linkage.

In a specific embodiment, E represents a chemical bond.

In another specific embodiment, E represents a methylene linkage.

Z preferably represents halogen, CN, CF_3, R^a, OR^a, SR^a, SO_2R^a, $SO_2NR^aR^b$, NR^aR^b, NR^aCOR^b, $NR^aCONR^aR^b$, NR^aSOR^a, $NR^aSO_2R^a$, COR^a, CO_2R^a, $CONR^aR^b$, $CR^a{=}NOR^b$ or a five- or six-membered heteroaromatic ring optionally bearing up to 2 substituents as defined previously.

Where the group Z represents an optionally substituted five-membered heteroaromatic ring, this is suitably an imidazole, pyrazole, thiazole, 1,2,3-triazole, 1,2,4-triazole or tetrazole ring, any of which optionally is substituted, typically by methyl. Such rings may be attached via a carbon atom or a nitrogen atom. Specific examples include pyrazol-3-yl, imidazol-2-yl, 1,2,4-triazol-3-yl and thiazol-2-yl.

Where the group Z represents an optionally substituted six-membered heteroaromatic ring, this is suitably a pyridine, pyrazine, pyrimidine, pyridazine or triazine ring, any of which optionally is substituted, typically by methyl or halogen. A specific example is 2-pyridyl.

R^a and R^b independently represent H or an optionally substituted hydrocarbon group as defined previously, or when linked through a nitrogen atom they may complete an optionally-substituted heterocyclic ring as defined previously. Hydrocarbon groups represented by R^a or R^b are preferably nonaromatic. Said hydrocarbon groups optionally bear up to 3 fluorine substituents and, in addition or as an alternative, optionally bear a substituent selected from Cl, Br, CN, OH, C_{1-4}alkoxy, C_{1-4}alkylthio, amino, C_{1-4}alkylamino and di(C_{1-4}alkyl)amino. Preferred substituents include F, OH and CN. Typically, R^a and R^b independently represent H; optionally substituted C_{1-6}alkyl (such as methyl, ethyl, isopropyl, tert-butyl, 2,2,2-trifluoroethyl, 2-cyanoethyl, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 1-hydroxy-1-methylethyl and 1-hydroxy-2,2,2-trifluoroethyl); optionally substituted C_{3-6}cycloalkyl (such as cyclopropyl, cyclobutyl and 1-hydroxycyclobutyl); C_{3-6}cycloalkylC_{1-4}alkyl (such as cyclopropylmethyl); or, when linked through a nitrogen atom, together represent the residue of a heterocyclic ring of 4, 5 or 6 members optionally bearing up to 3 substituents as defined previously. Such rings typically comprise at most two heteroatoms selected from N, O and S, inclusive of the nitrogen atom connecting R^a and R^b, for example azetidine, pyrrolidine, piperidine, tetrahydropyridine, piperazine, morpholine and thiomorpholine. Typical examples of cyclic groups represented by NR^aR^b include azetidin-1yl, 3,3-difluoroazetidin-1-yl, 3-hydroxyazetidin-1-yl, pyrrolidin-1-yl, 3-hydroxypyrrolidin-1-yl, 3-fluoropyrrolidin-1-yl, 2-trifluoromethylpyrrolidin-1-yl, piperidin-1-yl, 4-trifluoromethylpiperidin-1-yl, 3-trifluoromethylpiperidin-1-yl, 3-fluoropiperidin-1-yl, 3,3,-difluoropiperidin-1-yl, 4,4-difluoropiperidin-1-yl, 4-trifluoromethyl-1,2,3,6-tetrahydropyridin-1-yl, 4-methylpiperazin-1-yl, 3-oxo-piperazin-1-yl, morpholin-4-yl, 2,6-dimethylmorpholin-4-yl and 1,1-dioxo-thiomorpholin-4-yl.

When Z represents R^a, R^a very suitably represents H or optionally-substituted C_{1-6}alkyl or optionally substituted C_{3-6}cycloalkyl and E suitably represents a chemical bond.

Preferred identities for the moiety –E-Z include H, halogen, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 1-hydroxy-1-methylethyl, 1-hydroxycyclobutyl, CO_2Me, CO_2Et, $CONH_2$, CONHMe, $COCH_3$, NH_2, NHMe, NMe_2, $NHSO_2Me$, SO_2Me, CN, SO_2NH_2, pyrazol-3-yl, imidazol-2-yl and thiazol-3-yl.

The phenyl or pyridyl ring to which the moiety –E-Z is attached optionally bears up to two additional substituents R^2 as defined previously. Typically, n is 0 or 1 and hence not more than one R^2 group is present. Most preferably, n is 0. When present, preferred identities for R^2 include halogen (especially F), C_{1-4}alkyl (especially methyl) CN and $CONH_2$.

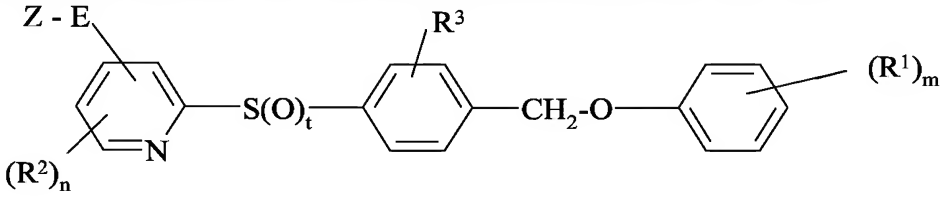
In an alternative embodiment, the moiety –E-Z and an R^2 substituent are attached at adjacent ring positions and combine to complete a fused imidazole group. Within this embodiment, A very suitably represents CH.

The moiety –E-Z and R^2 (if present) may be attached at any available ring position, including a carbon atom represented by A.

In formula I, m represents 0, 1, 2 or 3, but preferably represents 1 or 2. Each R^1 is preferably selected from halogen (preferably F or Cl, most preferably F), CN, hydroxymethyl, OH and C_{1-4}alkoxy (e.g. methoxy). Specific embodiments of $(R^1)_m$ include H, 2-fluoro, 3-fluoro, 4-fluoro, 2,4-difluoro, 3-cyano, 4-cyano, 2-chloro-4-fluoro, 4-fluoro-2-hydroxy, 4-chloro, 2-hydroxy, 2-cyano-4-fluoro, 4-fluoro-2-methoxy and 4-fluoro-2-hydroxymethyl. In a particular embodiment, $(R^1)_m$ represents 2-fluoro, 4-fluoro or 2,4-difluoro substitution of the phenyl ring.

R^3 preferably represents H, halogen (such as Br or Cl), CN or $CONH_2$. Most preferably, R^3 represents H.

In a particular embodiment, the invention provides a compound of formula II:



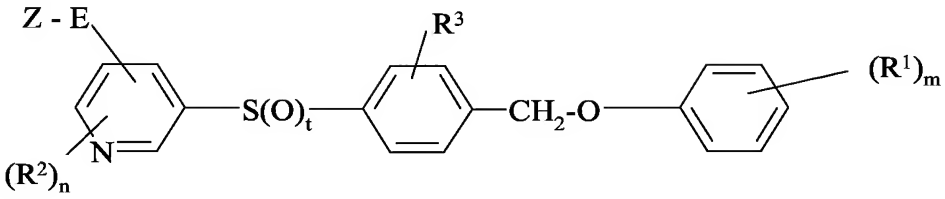
II

or a pharmaceutically acceptable salt thereof;

where all the variables have the same meanings and preferred identities as before.

Within this embodiment, the moiety Z-E- is preferably attached at a ring position which is adjacent to the point of attachment of the $-S(O)_t-$ moiety or adjacent to the ring nitrogen, most preferably adjacent to the point of attachment of the $-S(O)_t-$ moiety.

In another particular embodiment, the invention provides a compound of formula III:



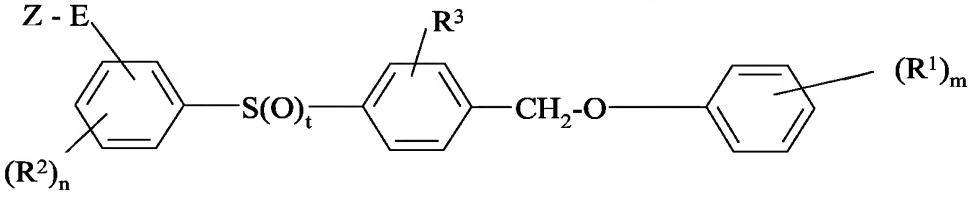
III

or a pharmaceutically acceptable salt thereof;

where all the variables have the same meanings and preferred identities as before.

Within this embodiment, the moiety Z-E- is preferably attached at a ring position which is adjacent to the point of attachment of the $-S(O)_t-$ moiety and/or adjacent to the ring nitrogen.

In a particular embodiment, the invention provides a compound of formula IV:



IV

or a pharmaceutically acceptable salt thereof;

where all the variables have the same meanings and preferred identities as before.

Specific compounds useful in this invention include those compounds exemplified hereinafter and their pharmaceutically acceptable salts.

The compounds of formula I have an activity as antagonists of the human 5-HT_{2A} receptor and hence find use in the treatment or prevention of disorders mediated by 5-HT_{2A} receptor activity.

The invention provides pharmaceutical compositions comprising one or more compounds of formula I and a pharmaceutically acceptable carrier. Preferably these compositions are in unit dosage forms such as tablets, pills, capsules, powders, granules, sterile parenteral solutions or suspensions, metered aerosol or liquid sprays, drops, ampoules, transdermal patches, auto-injector devices or suppositories; for oral, parenteral, intranasal, sublingual or rectal administration, or for administration by inhalation or insufflation. The principal active ingredient typically is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate and dicalcium phosphate, or gums, dispersing agents, suspending agents or surfactants such as sorbitan monooleate and polyethylene glycol, and other pharmaceutical diluents, e.g. water, to form a homogeneous preformulation composition containing a compound of the present invention, or a pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. Typical unit dosage forms contain from 1 to 100 mg, for example 1, 2, 5, 10, 25, 50 or 100 mg, of the active ingredient. Tablets or pills of the novel composition can be coated or otherwise compounded to

provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, liquid- or gel-filled capsules, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil or coconut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, poly(ethylene glycol), poly(vinylpyrrolidone) or gelatin.

The present invention also provides a compound of formula I or a pharmaceutically acceptable salt thereof for use in a method of treatment of the human body. Preferably the treatment is for a condition mediated by 5-HT_{2A} receptor activity.

The present invention further provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for treating or preventing a condition mediated by 5-HT_{2A} receptor activity.

Also disclosed is a method of treatment of a subject suffering from or prone to a condition mediated by 5-HT_{2A} receptor activity which comprises administering to that subject an effective amount of a compound according to formula I or a pharmaceutically acceptable salt thereof.

In one aspect of the invention, the condition mediated by 5-HT_{2A} receptor activity is sleep disorder, in particular insomnia. In a further aspect of the invention, the condition mediated by 5-HT_{2A} receptor activity is selected from psychotic disorders (such as schizophrenia), depression, anxiety, panic disorder, obsessive-compulsive disorder, pain, glaucoma, eating disorders (such as anorexia nervosa), dependency or acute toxicity associated with narcotic agents such as LSD or MDMA, and hot flushes associated with the menopause.

In the treatment envisaged herein, for example of insomnia or schizophrenia, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day but preferably once per day, for example before going to bed.

If desired, the compounds according to this invention may be co-administered with another sleep inducing or anti-schizophrenic or anxiolytic medicament. Such co-administration may be desirable where a patient is already established on sleep inducing or anti-schizophrenic or anxiolytic treatment regime involving other conventional medicaments. In particular, for the treatment of sleep disorders, the compounds of the invention may be co-administered with a $GABA_A$ receptor agonist such as gaboxadol, or

with a short term and/or rapid-onset hypnotic such as zolpidem, or a benzodiazepine, a barbiturate, a prokineticin modulator, an antihistamine, trazodone, or derivative of trazodone as disclosed in WO 03/068148.

According to a further aspect of the invention, there is provided the combination of a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol for use in treatment or prevention of sleep disorders, schizophrenia or depression.

Also according to the invention, there is provided a method of treatment or prevention of sleep disorders, schizophrenia or depression comprising administering to a subject in need thereof a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof in combination with gaboxadol.

As used herein, the expression "in combination with" requires that therapeutically effective amounts of both a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol are administered to the subject, but places no restriction on the manner in which this is achieved. Thus, the two species may be combined in a single dosage form for simultaneous administration to the subject, or may be provided in separate dosage forms for simultaneous or sequential administration to the subject. Sequential administration may be close in time or remote in time, e.g. one species administered in the morning and the other in the evening. The separate species may be administered at the same frequency or at different frequencies, e.g. one species once a day and the other two or more times a day. The separate species may be administered by the same route or by different routes, e.g. one species orally and the other parenterally, although oral administration of both species is preferred, where possible.

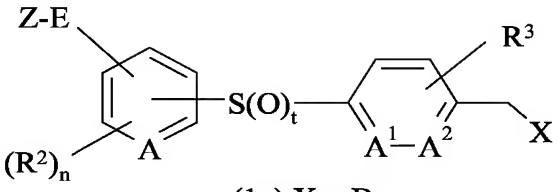
According to a further aspect of the invention there is provided a pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol.

The invention further provides the use, for the manufacture of a medicament for treatment or prevention of sleep disorders, schizophrenia or depression, of a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and gaboxadol.

The invention further provides a kit comprising a first medicament comprising a compound of formula I or a pharmaceutically acceptable salt or hydrate thereof and a second medicament comprising gaboxadol together with instructions for administering said medicaments sequentially or simultaneously to a patient suffering from a sleep disorder, schizophrenia or depression.

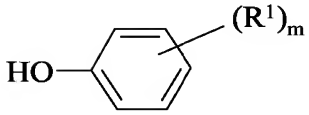
As used herein, the term "gaboxadol" is inclusive of 4,5,6,7-tetrahydroisoxazolo[5,4-*c*]pyridin-3-ol in free base or zwitterionic form and also of pharmaceutically acceptable acid addition salts thereof such as the hydrochloride salt. Most suitably, gaboxadol is in the form of a crystalline monohydrate of the zwitterionic form.

Compounds of formula I may be prepared by reaction of a benzyl bromide of formula (1a) with a phenol of formula (2):



(1a) X = Br

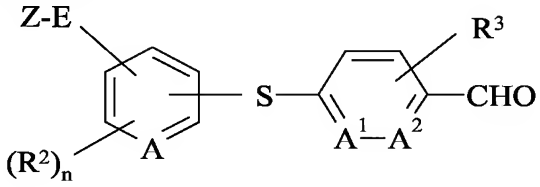
(1b) X = OH



(2)

where m, n, t, A, A^1, A^2, Z, E, R^1, R^2 and R^3 have the same meanings as before. The reaction may be carried out at elevated temperature (e.g. about 100°C) in DMF in the presence of base (e.g. an inorganic base such as potassium carbonate).

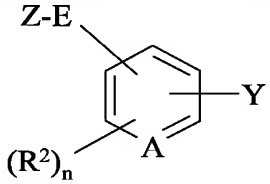
Bromides (1a) are available by treatment of alcohols (1b) with a brominating agent such as phosphorus tribromide or a combination of carbon tetrabromide and triphenylphosphine. Alcohols (1b) are available by reduction of aldehydes (3):



(3)

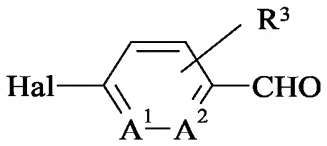
where n, A, A^1, A^2, Z, E, R^1, and R^3 have the same meanings as before, followed by oxidation of the thioether group. The reduction is suitably carried out using sodium borohydride, e.g. in a methanol – THF mixture at ambient temperature. Oxidation using one molar equivalent of oxidant gives the sulphoxides (t = 1 in formula (1b)) while use of excess oxidant gives the sulphones (t = 2 in formula (1b)). Suitable oxidants include Oxone® and peroxyacids such as m-chloroperoxybenzoic acid. A preferred oxidant for use in preparing the sulphones is hydrogen peroxide in acetic acid in the presence of sodium tungstate.

Compounds (3) are available by reaction of thiols (4a) with halobenzaldehydes (5):



(4a) Y = SH

(4b) Y = $SO_2^-Na^+$

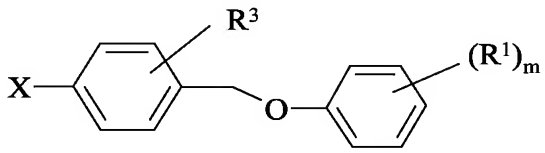


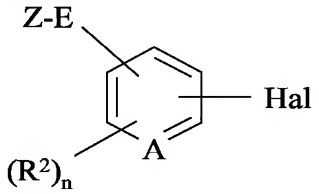
(5)

where Hal represents halide (eg. Cl, F) and n, A, A^1, A^2, Z, E, R^1, and R^3 have the same meanings as before. The reaction takes place at elevated temperature (e.g. 120°C) in the presence of base (preferably an inorganic base such as potassium carbonate) in DMSO.

An alternative route to alcohols (1b) in which t is 2 comprises reaction of fluorobenzaldehydes (5) with sulphinate salts (4b), followed by reduction of the aldehyde group as before. The reaction takes place in DMSO solution at elevated temperature (e.g. about 100 – 130°C) (Ulman *et al, J.Org.Chem.* (1989), **54**(19), 4691-2).

An alternative route to compounds of formula I in which t is 2 and A^1 and A^2 are both CH comprises reaction of a sulphinate salt of formula (6a) with an aryl bromide or iodide of formula (7):





(6a) $X = SO_2^-Na^+$

(6b) $X = SCH_3$

(6c) $X = Br$

(7)

where Hal represents Br or I and m, n, A, Z, E, R^1, R^2 and R^3 have the same meanings as before. The reaction takes place in DMSO at elevated temperature (e.g. about 130°C) in the presence of CuI.

The sulphinate salts (6a) are available by treatment of the corresponding thioanisoles (6b) sequentially with an oxidising agent (e.g. m-chloroperoxybenzoic acid), sodium acetate in acetic anhydride, magnesium peroxyphthalate, and sodium hydroxide.

Thioanisoles (6b) are obtainable by coupling of a phenol (2) with the appropriate 4-(hydroxymethyl)thioanisole under standard Mitsonobu conditions (e.g. using diisopropylazodicarboxylate and Ph_3P in THF at 0°C).

An alternative route to sulphinate salts (6a) comprises coupling of the bromo-derivative (6c) with methyl 3-mercaptopropionate, oxidation of the resulting thioether to the corresponding sulphone, and treatment of the resulting arylsulphonylpropionate methyl ester with sodium methoxide to generate the sulphinate salt. Suitable conditions for this process are described in the examples section herein.

Where they are not themselves commercially available, the starting materials and reagents described above may be obtained from commercially available precursors by means of well known synthetic procedures and/or the methods disclosed in the Examples section herein.

It will be appreciated that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further desired compound of formula I using techniques known from the art. For example, a bromo substituent represented by Z-E-, R^1, R^2 or R^3 may be replaced by cyano by treatment with copper(I) cyanide in the presence of 1-methyl-2-pyrrolidinone (NMP), or with zinc cyanide in the presence of tetrakis(triphenylphosphine)palladium(0). The cyano group thereby obtained may in turn be converted into carboxamido by heating in mineral acid, e.g. 85% sulphuric acid at 100 C, or by treatment with potassium trimethylsilanolate, typically in tetrahydrofuran at reflux, or by treatment with alkaline hydrogen peroxide. Similarly, a fluoro substituent represented by Z-E- or R^3 may be replaced by NR^aR^b or an optionally substituted N-linked heteroaryl moiety, e.g. imidazol-1-yl, pyrazol-1-yl, 1,2,3-triazol-1-yl or 1,2,4-triazol-1-yl, by treatment with HNR^aR^b or the appropriate optionally substituted N-containing heteroaryl compound, typically with heating in DMSO. Similarly, a bromo substituent represented by Z-E- may be replaced by an optionally substituted C-linked five-membered heteroaromatic ring, e.g. 2-methyltetrazol-5-yl or 1-methyl-1,2,4-triazol-5-yl, by reaction with a

tributylstannyl derivative of the appropriate heteroaromatic compound, e.g. 2-methyl-5-tributylstannyltetrazole or 1-methyl-5-tributylstannyl-1,2,4-triazole, in the presence of a transition metal catalyst such as tetrakis(triphenylphosphine)palladium(0), typically with heating in a solvent such as *N,N*-dimethylformamide. A cyano substituent represented by Z-E- may be converted to CHO by diisobutylaluminium hydride (DIBAL-H) reduction and hydrolysis. A CHO substituent represented by Z-E- may be converted to $CH_2NR^aR^b$ by treatment with HNR^aR^b and sodium triacetoxyborohydride or sodium cyanoborohydride. A substituent COR^a represented by Z-E- may be converted to $CH(OH)R^a$ by reduction (e.g. using sodium borohydride) or to $CR^a(OH)R^b$ by treatment with R^bMgHal where Hal is Cl, Br or I. Compounds in which Z-E- take the form $Z\text{-}(CH_2)_y\text{-}O\text{-}$ where y is 1, 2, 3, or 4 may be formed by treating the corresponding compounds in which Z-E- is F with $Z\text{-}(CH_2)_yOH$ in the presence of strong base.

Such processes may also be used to prepare appropriately-substituted precursors of the compounds of Formula I and/or to manipulate the identity of R^3. A preferred route to compounds (7) wherein A represents N, Hal is in the 2-position and Z-E- represents 1-hydroxyalkyl or 1-hydroxycycloalkyl attached to the 3-position comprises treatment of 2-bromopyridine with lithium diisopropylamide followed by the appropriate ketone.

Where the above-described processes for the preparation of the compounds of use in the invention give rise to mixtures of stereoisomers, these isomers may be separated by conventional techniques such as preparative chromatography. The compounds may be prepared in racemic form, or individual enantiomers may be prepared either by enantiospecific synthesis or by resolution. The compounds may, for example, be resolved into their component enantiomers by standard techniques such as preparative HPLC, or the formation of diastereomeric pairs by salt formation with an optically active acid, such as di-*p*-toluoyl-D-tartaric acid and/or di-*p*-toluoyl-L-tartaric acid, followed by fractional crystallization and regeneration of the free base. The compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene & P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

Compounds were tested for their binding to the $5\text{-}HT_{2A}$ receptor and to other receptors such as $5\text{-}HT_{2C}$ and IKr using the methodology described in Fletcher *et al, J. Med. Chem.*, 2002, **45**, 492-503.

EXAMPLES

Intermediate 1

Sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate

Method 1

Step 1: 2,4-Difluoro-1-{[4-(methylthio)benzyl]oxy}benzene

To a solution of 2,4-difluorophenol (13 g, 100 mmol), 4-hydroxymethyl thioanisole (15.4 g, 100 mmol) and triphenylphosphine (28.93 g, 110 mmol) in THF (300 mL) at 0 °C was added diisopropylazodicarboxylate (22.22 g, 110 mmol). The reaction was allowed to warm to room temperature and stirred for 16 h. The solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 12% ethyl acetate/isohexane, followed by crystallisation from isohexane to give the title compound as a solid (13.5 g, 51%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (2 H, d, J 8.2 Hz), 7.26 (2 H, d, J 8.3 Hz), 6.94-6.84 (2 H, m), 6.76-6.72 (1 H, m), 5.05 (2 H, s), 2.49 (3 H, s).

Step 2: 2,4-difluoro-1-{[4-(methylsulfinyl)benzyl]oxy}benzene

2,4-Difluoro-1-{[4-(methylthio)benzyl]oxy}benzene (Step 1, 13.5 g, 50.8 mmol) was dissolved in DCM (500 mL) and cooled to 0 °C. 3-Chloroperoxybenzoic acid (77%, 72.5 ml, 55.8 mmol) was added cautiously and the reaction was stirred for 30 min. Calcium hydroxide (5.6 g, 76.13 mmol) was added to the reaction and stirred for 15 min. The mixture was filtered through Hyflo® and the filtrate evaporated *in vacuo* to give the title compound as a solid (14.3 g, 100%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.64 (2 H, d, J 8.2 Hz), 7.57 (2 H, d, J 8.2 Hz), 6.95-6.89 (1 H, m), 6.87-6.83 (1 H, m), 6.76-6.72 (1 H, m), 5.11 (2 H, s), 2.70 (3 H, s).

Step 3: ({4-[(2,4-Difluorophenoxy)methyl]phenyl}sulfonyl)methyl acetate

2,4-difluoro-1-{[4-(methylsulfinyl)benzyl]oxy}benzene (Step 2, 14.3 g, 50.7 mmol) was dissolved in acetic anhydride (160 mL) and sodium acetate (15.59 g, 190.16 mmol) was added. The reaction was heated at reflux for 2 h. The solvent was removed *in vacuo* and the residue azeotroped with toluene. The residue was suspended in DCM (160 mL) and MeOH (80 mL) and cooled to 0 °C, before adding magnesium monoperoxyphthalate (90%, 32 g, 58.32 mmol). The reaction was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched by adding saturated $NaHCO_3$ (300 mL) and water (300 mL) and then diluting with EtOAc. The organic extract was washed with $NaHCO_3$ and water, dried and evaporated. The residue was purified by flash column chromatography on silica, eluting with 20-35% ethyl acetate/isohexane to give the title compound as a solid (7.65g, 42%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.94 (2 H, d, J 8.3 Hz), 7.65 (2 H, d, J 8.4 Hz), 6.95-6.87 (2 H, m), 6.79-6.75 (1 H, m), 5.18 (2 H, s), 5.14 (2 H, s), 2.07 (3 H, s).

Step 4: Sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate

({4-[(2,4-Difluorophenoxy)methyl]phenyl}sulfonyl)methyl acetate (Step 3, 7.65 g, 23.6 mmol) was dissolved in a mixture of THF (80 mL) and MeOH (40 mL). Sodium hydroxide (4M, 5.9 ml, 23.6 mmol) was added. The reaction was stirred for 1 h. The solvent was removed *in vacuo*. The residue was azeotroped with EtOH and triturated with hot EtOH to yield the title compound as a solid (7.1g, 98%). ^{1}H

NMR (500 MHz, DMSO): δ 7.46 (2 H, d, J 7.5 Hz), 7.36 (2 H, d, J 7.8 Hz), 7.28-7.20 (2 H, m), 6.99-6.95 (1 H, m), 5.12 (2 H, s); *m/z* (ES^+) 307 [MH^+].

Method 2

Step 1: 1-[(4-bromobenzyl)oxy]-2,4-difluorobenzene

To a solution of 4-bromo benzylbromide (9.5 g, 38 mmol) and 2,4-difluorophenol (4.0 ml, 42 mmol) in anhydrous DMF (114 mL) was added potassium carbonate (7.8 g, 57 mmol). The mixture was heated to 80 °C for 12 h. The reaction was partitioned between EtOAc and aqueous saturated $NaHCO_3$, the organics were washed with 1M NaOH, water and brine successively; dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 5% ethyl acetate/isohexane, to yield a white solid (9.8 g, 78%). ^1H NMR (500 MHz, DMSO): δ 7.60 (2H, d, J 8.3), 7.41 (2H, d, J 8.3), 7.31-7.23 (2H, m), 7.01 (1H, t, J 8.7), 5.14 (2H, s).

Step 2: methyl 3-({4-[(2,4-difluorophenoxy)methyl]phenyl}thio)propanoate

To a degassed solution of 1-[(4-bromobenzyl)oxy]-2,4-difluorobenzene (9.8 g, 32.6 mmol), diisopropylethylamine (11.4 mL, 65.3 mmol) and methyl 3-mercaptopropionate (3.9 mL, 35.9 mmol) in anhydrous dioxane (165 mL) was added tris(dibenzylideneacetone) dipalladium (745 mg, 0.82 mmol) and 9,9-dimethyl-4,5-bis(diphenylphosphino) xanthene (945 mg, 1.63 mmol). The reaction was heated to 110 °C for 18 h. On cooling, the reaction was partitioned between EtOAc and water, the organics were washed water and brine successively; dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 25% ethyl acetate/isohexane, to yield a yellow solid (11.1 g, 98%). ^1H NMR (500 MHz, DMSO): δ 7.38 (4H, q, J 9.1), 7.30-7.23 (2H, m), 7.03-6.99 (1H, m), 5.12 (2H, s), 3.59 (3H, s), 3.18 (2H, t, J 7.0), 2.63 (2H, t, J 7.0).

Step 3: methyl 3-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)propanoate

A solution of methyl 3-({4-[(2,4-difluorophenoxy)methyl]phenyl}thio)propanoate (11.1 g, 32 mmol) in DCM (162 mL) was cooled to 0 °C, and 3-chloroperoxybenzoic acid (21.5 g, 96 mmol) was added. The reaction was warmed to ambient temperature and stirred for 12 h. The white suspension was diluted with DCM (50 mL) and calcium hydroxide (8.9 g, 120 mmol) was added. The white suspension was stirred for 1 h, then filtered through a pad of Hylfo®. The resultant liquors were reduced in vacuo and purified by flash column chromatography on silica, eluting with 55% ethyl acetate/isohexane, to yield a white solid (9.8 g, 82%). ^1H NMR (400 MHz, DMSO): δ 7.93 (2H, d, J 8.3), 7.72 (2H, d, J 8.2), 7.39-7.25 (2H, m), 7.05-7.01 (1H, m), 5.31 (2H, s), 3.58 (2H, t, J 7.2), 3.51 (3H, s), 2.64 (2H, t, J 7.2).

Step 4: Sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate

To a solution of methyl 3-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)propanoate (9.8 g, 26 mmol) in a 4:1 mixture of THF/MeOH (260 mL) was added sodium methoxide powder (2.1 g, 39 mmol). A precipitate formed on stirring, and the reaction was complete in 30 min. The volatiles were evaporated and

the resultant residue was diluted with water (90 mL) and filtered. The filter cake was washed with cold water (3 x 200 mL) and ether (100 mL); dried at the pump for 2 h, followed by vacuum oven for 12 h; to yield the title compound as a white solid (6.7 g, 84%). ^{1}H NMR (500 MHz, DMSO): δ 7.48 (2H, d, J 7.6), 7.38 (2H, d, J 7.7), 7.29-7.22 (2H, m), 7.00-6.98 (1H, m), 5.14 (2H, s); *m/z* (ES^+) 307 [MH^+].

Example 1

1-fluoro-2-{[4-(phenylsulfonyl)benzyl]oxy}benzene

Step 1: 1-(bromomethyl)-4-(phenylsulfonyl)benzene

4-(Phenylsulfonyl)benzaldehyde (prepared according to the method of Ulman *et al.*, *J. Org. Chem.* (1989), **54(19)**, 4691-2; 12.3 g, 50 mmol) was dissolved in THF and MeOH was added, followed by careful addition of sodium borohydride (2.0 g, 52.9 mmol). The reaction was stirred for 1 h before pouring into water and extracting with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo* to give [4-(phenylsulfonyl)phenyl]methanol. This was treated with phosphorus tribromide and heated to reflux for 16 h. The cooled reaction mixture was poured onto ice and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with dichloromethane, to give to give the title compound as a solid (10.1 g, 65%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.96-7.90 (4 H, m), 7.59-7.56 (1 H, m), 7.52-7.49 (4 H, m).

Step 2: 1-fluoro-2-{[4-(phenylsulfonyl)benzyl]oxy}benzene

1-(Bromomethyl)-4-(phenylsulfonyl)benzene (Step 1, 78 mg, 0.25 mmol), 2-fluorophenol (0.05 mL, 0.6 mmol), potassium carbonate (69 mg, 0.50 mmol) and DMF (1 mL) were combined and the mixture stirred at 100 °C for 18 h. On cooling, water (4 mL) and aqueous sodium hydroxide (4N, 1 mL) were added sequentially to the vigorously stirred mixture causing precipitation. The solid was isolated by filtration and washed with water (50 mL), then dried by a fast stream of air for 10 h to afford the title compound as an off-white amorphous solid. ^{1}H NMR (360 MHz, DMSO): δ 8.01-7.95 (4 H, m), 7.71-7.61 (5 H, m), 7.25-7.09 (3 H, m), 6.98-6.92 (1 H, m), 5.28 (2 H, s); *m/z* (ES^+) 384 [$(M+MeCN)^+$].

Examples 2-7 were prepared as for Example 1, using the appropriate phenol in Step 2.

Example 2

1-fluoro-3-{[4-(phenylsulfonyl)benzyl]oxy}benzene

^{1}H NMR (360 MHz, DMSO): δ 8.01-7.95 (4 H, m), 7.72-7.60 (5 H, m), 7.36-7.28 (1 H, m), 6.92-6.76 (3 H, m), 5.22 (2 H, s); *m/z* (ES^+) 384 [$(M+MeCN)^+$].

Example 3

1-fluoro-4-{[4-(phenylsulfonyl)benzyl]oxy}benzene

^{1}H NMR (360 MHz, DMSO): δ 8.00-7.94 (4 H, m), 7.72-7.60 (5 H, m), 7.15-7.09 (2 H, m), 7.04-6.98 (2 H, m), 5.18 (2 H, s); *m/z* (ES^+) 384 [$(M+MeCN)^+$].

Example 4

1-chloro-2-{[4-(phenylsulfonyl)benzyl]oxy}benzene

^{1}H NMR (360 MHz, DMSO): δ 7.99-7.93 (4 H, m), 7.69-7.57 (5 H, m), 7.42 (1 H, dd, J 1.6, 7.9 Hz), 7.25 (1 H, dd, J 1.4, 7.3 Hz), 7.16 (1 H, dd, J 1.4, 8.3 Hz), 6.97-6.91 (1 H, m), 5.28 (2 H, s); *m/z* (ES^+) 359 [MH^+].

Example 5

1-chloro-3-{[4-(phenylsulfonyl)benzyl]oxy}benzene

^{1}H NMR (400 MHz, DMSO): δ 7.98-7.94 (4 H, m), 7.69-7.59 (5 H, m), 7.30 (1 H, t, J 8.1 Hz), 7.09 (1 H, t, J 2.2 Hz), 7.01-6.95 (2 H, m), 5.22 (2 H, s); *m/z* (ES^+) 359 [MH^+].

Example 6

1-chloro-4-{[4-(phenylsulfonyl)benzyl]oxy}benzene

^{1}H NMR (400 MHz, DMSO): δ 7.97-7.91 (4 H, m), 7.67-7.57 (5 H, m), 7.32-7.28 (2 H, m), 7.01-6.97 (2 H, m), 5.17 (2 H, s); *m/z* (ES^+) 359 [MH^+].

Example 7

1-(phenoxymethyl)-4-(phenylsulfonyl)benzene

^{1}H NMR (400 MHz, DMSO): δ 7.97-7.91 (4 H, m), 7.67-7.57 (5 H, m), 7.28-7.22 (2 H, m), 6.97-6.89 (3 H, m), 5.17 (2 H, s); *m/z* (ES^+) 325 [MH^+].

Example 8

2-({4-[(4-fluorophenoxy)methyl]phenyl}sulfonyl)benzonitrile

Step 1: 4-[(2-bromophenyl)thio]benzaldehyde

4-fluorobenzaldehyde (10 mL, 93 mmol), 2-bromobenzenethiol (12 mL, 102 mmol) and potassium carbonate (15.4 g, 111 mmol) were combined in DMSO (50 mL) under nitrogen and heated to 210 °C for 2 h. The cooled reaction mixture was partitioned between water and ethyl acetate. The organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 10% ethyl acetate/isohexane, to give to give the title compound as a solid (23.83 g, 87%). ^{1}H NMR (360 MHz, DMSO): δ 9.97 (1 H, s), 7.89-7.82 (3 H, m), 7.55-7.33 (5 H, m).

Step 2: {4-[(2-bromophenyl)sulfonyl]phenyl}methanol

To a solution of 4-[(2-bromophenyl)thio]benzaldehyde (Step 1, 17 g, 58 mmol) in EtOH under nitrogen (290 mL) was added sodium borohydride (21 g, 580 mmol). The reaction was stirred at room temperature for 1 h. The solvent was removed *in vacuo* and the residue partitioned between EtOAc and water. The

organic layer was dried over Na_2SO_4 and the solvent removed *in vacuo* to yield {4-[(2-bromophenyl)thio]phenyl}methanol. This was dissolved in acetic acid (120 mL), hydrogen peroxide (24 mL, 290 mmol) and catalytic sodium tungstate (50 mg) were added and the reaction was stirred overnight at room temperature. Water and EtOAc were added and the aqueous layer extracted with EtOAc (x2). The combined organic layers were washed with aqueous $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was azeotroped with xylene then 2 g removed to be purified by flash column chromatography on silica, eluting with 60% ethyl acetate/isohexane, to give a white solid. ^{1}H NMR (400 MHz, DMSO): δ 8.31 (1 H, dd, J 1.6, 7.9 Hz), 7.86 (2 H, d, J 8.4 Hz), 7.80 (1 H, dd, J 1.2, 7.9 Hz), 7.72-7.68 (1 H, m), 7.62-7.58 (1 H, m), 7.54 (2 H, d, J 8.4 Hz), 5.43 (1 H, t, J 5.7 Hz), 4.58 (2 H, d, J 5.5 Hz).

Step 3: 2-{[4-(hydroxymethyl)phenyl]sulfonyl}benzonitrile

A solution of {4-[(2-bromophenyl)sulfonyl]phenyl}methanol (Step 2, 202 g, 6.72 mmol) and zinc cyanide (0.79 g, 6.72 mmol) in DMF (13.5 mL) was degassed and tetrakis(triphenylphosphine)palladium(0) (0.77 g, 0.67 mmol) added. The reaction was heated to 85 °C under nitrogen overnight. Further zinc cyanide (0.79 g, 6.72 mmol) and tetrakis(triphenylphosphine)palladium(0) (0.77 g, 0.67 mmol) were added and heating continued for 4 h. The cooled reaction mixture was partitioned between EtOAc and water, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica, eluting with 80% ethyl acetate/isohexane, to give to give the title compound as a solid (560 mg, 31%). ^{1}H NMR (360 MHz, DMSO): δ 8.30 (1 H, t, J 4.4 Hz), 8.08 (1 H, dd, J 0.9, 7.4 Hz), 8.00-7.92 (3 H, m), 7.90-7.84 (1 H, m), 7.58 (2 H, d, J 8.2 Hz), 5.42 (1 H, t, J 5.7 Hz), 4.56 (2 H, d, J 5.7 Hz).

Step 4: 2-{[4-(bromomethyl)phenyl]sulfonyl}benzonitrile

To a solution of 2-{[4-(hydroxymethyl)phenyl]sulfonyl}benzonitrile (Step 3, 560 mg, 2.05 mmol) and triphenylphosphine (591 mg, 2.26 mmol) in DCM (10 mL) at 0 °C was added carbon tetrabromide (815 mg, 2.46 mmol). The reaction was stirred at 0 °C for 1.5 h. The reaction mixture was diluted with DCM, washed with water, dried over Na_2SO_4 and evaporated. The residue was purified by flash column chromatography on silica, eluting with 40% ethyl acetate/isohexane, to give to give the title compound as a solid (330 mg, 47%). ^{1}H NMR (360 MHz, DMSO): δ 8.32 (1 H, dd, J 0.9, 8.0 Hz), 8.10 (1 H, d, J 7.5 Hz), 8.01-7.95 (3 H, m), 7.92-7.86 (1 H, m), 7.71 (2 H, d, J 8.4 Hz), 4.73 (2 H, s).

Step 5: 2-({4-[(4-fluorophenoxy)methyl]phenyl}sulfonyl)benzonitrile

Potassium carbonate (69 mg, 0.5 mmol) and 4-fluorophenol (56 mg, 0.5 mmol) were added to a solution of 2-{[4-(bromomethyl)phenyl]sulfonyl}benzonitrile (Step 4, 85 mg, 0.25 mmol) in DMF (1 mL) and the reaction heated to 100 °C for 5 h. The reaction mixture was diluted with sodium hydroxide solution and extracted with EtOAc. The organic layer was dried over Na_2SO_4 and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 40% ethyl acetate/isohexane, to give the title compound as a white solid (24 mg, 26%). ^{1}H NMR (400 MHz, DMSO): δ 8.33 (1 H, dd, J 1.1, 7.9

Hz), 8.11 (1 H, dd, J 1.2, 7.6 Hz), 8.03-7.99 (3 H, m), 7.92-7.88 (1 H, m), 7.72 (2 H, d, J 8.5 Hz), 7.14-7.08 (2 H, m), 7.04-6.98 (2 H, m), 5.19 (2 H, s).

Example 9

2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)benzonitrile

Prepared according to the method of Example 8 using 2,4-difluorophenyl in step 5. ^{1}H NMR (500 MHz, DMSO): δ 8.33 (1 H, d, J 7.9 Hz), 8.10 (1 H, d, J 7.6 Hz), 8.04-7.98 (3 H, m), 7.89 (1 H, t, J 7.6 Hz), 7.72 (2 H, d, J 8.4 Hz), 7.31-7.21 (2 H, m), 6.99 (1 H, t, J 8.6 Hz), 5.26 (2 H, s); *m/z* (ES^+) 386 [MH^+].

Example 10

2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)benzamide

A solution of 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)benzonitrile (Example 9, 150 mg, 0.39 mmol) in DMSO (10 mL) was added to a solution of potassium carbonate (107 mg, 0.77 mmol) in water (0.5 mL). Hydrogen peroxide (27% in water, 0.2 mL, 1.56 mmol) added dropwise and the reaction stirred at room temperature for 2 h. The reaction mixture was partitioned between EtOAc and sodium sulfite solution. The organic layer was washed with brine, dried over Na_2SO_4 and evaporated *in vacuo* to give the title compound (109 mg, 70%). ^{1}H NMR (500 MHz, DMF): δ 8.32 (1 H, dd, J 1.3, 7.9 Hz), 8.27 (2 H, d, J 8.4 Hz), 8.21 (1 H, s), 7.97-7.93 (1 H, m), 7.90-7.86 (3 H, m), 7.82 (1 H, s), 7.70 (1 H, dd, J 1.4, 7.5 Hz), 7.56-7.44 (2 H, m), 7.26-7.20 (1 H, m), 5.48 (2 H, s); *m/z* (ES^+) 404 [MH^+].

Example 11

2-({4-[(2-fluorophenoxy)methyl]phenyl}sulfonyl)benzamide

Prepared from 2-({4-[(2-fluorophenoxy)methyl]phenyl}sulfonyl)benzonitrile (prepared according to the method of Example 8 using 2-fluorophenol in step 5) according to the method of Example 10. ^{1}H NMR (360 MHz, DMSO): δ 8.04 (1 H, dd, J 1.0, 7.8 Hz), 8.00 (2 H, d, J 8.4 Hz), 7.93 (1 H, s), 7.70-7.64 (1 H, m), 7.63-7.57 (3 H, m), 7.54 (1 H, s), 7.42 (1 H, dd, J 1.3, 7.4 Hz), 7.20-7.14 (2 H, m), 7.08-7.04 (1 H, m), 6.93-6.87 (1 H, m), 5.22 (2 H, s); *m/z* (ES^+) 386 [MH^+].

Example 12

2-({4-[(4-fluorophenoxy)methyl]phenyl}sulfonyl)benzamide

Prepared from 2-({4-[(4-fluorophenoxy)methyl]phenyl}sulfonyl)benzonitrile (Example 8, step 5) according to the method of Example 10. ^{1}H NMR (400 MHz, DMSO): δ 8.08 (1 H, dd, J 1.1, 7.9 Hz), 8.02 (2 H, d, J 8.4 Hz), 7.96 (1 H, s), 7.72-7.68 (1 H, m), 7.65-7.61 (3 H, m), 7.57 (1 H, s), 7.45 (1 H, dd, J 1.3, 7.4 Hz), 7.13-7.07 (2 H, m), 7.02-6.98 (2 H, m), 5.16 (2 H, s); *m/z* (ES^+) 386 [MH^+].

Example 13

[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)phenyl]methanol

Step 1: 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)benzaldehyde

Diisobutylaluminium hydride (1.5M in toluene, 0.13 mL, 0.195 mmol) was added dropwise to a solution of 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)benzonitrile (Example 9, 72 mg, 0.187 mmol) in dichloromethane (1 mL) and toluene (0.6 mL) at -78 °C. The reaction was allowed to warm to 0 °C and stirred for 30 min, then quenched with MeOH (1 drop), 2M HCl (2 mL) and DCM (2 mL) and stirred vigorously. The mixture was partitioned between DCM and water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 50% ethyl acetate/isohexane, to give the title compound as a solid. ^{1}H NMR (400 MHz, DMSO): δ 10.67 (1 H, s), 8.18 (1 H, d, J 7.6 Hz), 8.04 (2 H, d, J 8.4 Hz), 7.95-7.89 (3 H, m), 7.70 (2 H, d, J 8.4 Hz), 7.32-7.20 (2 H, m), 7.01-6.97 (1 H, m), 5.26 (2 H, s).

Step 2: [2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)phenyl]methanol

Sodium borohydride (10 mg, 0.26 mmol) was added to a solution of 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)benzaldehyde (Step 1, 17 mg, 0.04 mmol) in MeOH (2 mL) and dichloromethane (0.5 mL). The reaction was stirred for 1 h. The solvent was removed *in vacuo* and the residue partitioned between DCM and water. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was crystallised from Et_2O to give the title compound (19 mg, 26%). ^{1}H NMR (500 MHz, DMSO): δ 8.07 (1 H, d, J 8.0 Hz), 7.88 (2 H, d, J 8.3 Hz), 7.77-7.70 (2 H, m), 7.66 (2 H, d, J 8.2 Hz), 7.55 (1 H, t, J 7.7 Hz), 7.31-7.27 (1 H, m), 7.26-7.20 (1 H, m), 6.99 (1 H, t, J 8.6 Hz), 5.38 (1 H, t, J 5.7 Hz), 5.24 (2 H, s), 4.68 (2 H, d, J 5.8 Hz); *m/z* (ES^+) 391 [MH^+].

Example 14

Methyl 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)nicotinate

Sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate (Intermediate 1; 0.32 g, 1.05 mmol), 2-bromonicotinic acid (0.21 g, 1.05 mmol) and copper iodide (0.62 g, 3.14 mmol) were suspended in DMSO (2 mL) and stirred at room temperature then heated to 130 °C for 1 h. The cooled reaction mixture was diluted with ethyl acetate, poured into saturated ammonium chloride solution and filtered through Hyflo®. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was suspended in DCM (25 mL) and oxalyl chloride (0.66 g, 5.23 mmol) was added with a drop of DMF. When gas evolution had ceased, the reaction mixture was evaporated and the residue azeotroped with toluene to yield 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)nicotinyl chloride (0.15g, 34%). 210 mg of this was refluxed in dry MeOH for 1 h. The solvent was removed and the residue was taken up into EtOAc and washed with saturated $NaHCO_3$ solution. The organic extract was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica, eluting with 35% ethyl acetate/isohexane to give the title compound (0.135 g, 65%). ^{1}H NMR (500 MHz, DMSO): δ 8.76 (1 H, dd, J 1.4, 4.7 Hz), 8.22 (1 H, dd, J 1.3, 7.8 Hz), 7.97 (2 H, d, J 8.3 Hz), 7.77 (1 H, dd, J 4.6, 7.7 Hz), 7.71 (2 H, d, J 8.3 Hz), 7.32-7.22 (2 H, m), 7.00 (1 H, t, J 8.6 Hz), 5.27 (2 H, s), 3.92 (3 H, s); *m/z* (ES^+) 420 [MH^+].

Example 15

2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)nicotinamide

Step 1: 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)nicotinaldehyde

2-Bromonicotinaldehyde (1 g, 5.41 mmol), sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate (Intermediate 1; 1.65 g, 5.41 mmol) and copper iodide (3.23 g, 16.22 mmol) were suspended in DMSO (10 mL) and heated to 130 °C for 1 h. The cooled reaction mixture was diluted with EtOAc, poured into saturated ammonium chloride solution and filtered through Hyflo®. The organic extract was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica, eluting with 35% ethyl acetate/isohexane to give the title compound (0.85g, 40%). ^{1}H NMR (500 MHz, DMSO): δ 10.88 (1 H, s), 8.81 (1 H, dd, J 1.5, 4.6 Hz), 8.31 (1 H, dd, J 1.5, 7.9 Hz), 8.08 (2 H, d, J 8.2 Hz), 7.83 (1 H, dd, J 4.6, 7.8 Hz), 7.73 (2 H, d, J 8.2 Hz), 7.33-7.23 (2 H, m), 7.01 (1 H, t, J 8.7 Hz), 5.30 (2 H, s).

Step 2: 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)nicotinamide

2-({4-[(2,4-Difluorophenoxy)methyl]phenyl}sulfonyl)nicotinaldehyde (Step 1, 200 mg, 0.51 mmol) was dissolved in ammonium hydroxide (3 mL) and THF (5 mL) and iodine (0.14 g, 0.57 mmol) was added. The reaction was stirred for 16 h at room temperature. Hydrogen peroxide (35%, 2 mL) was added and the reaction was stirred for one hour before pouring into water and extracting with ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate, to give the title compound (35 mg, 17%). ^{1}H NMR (500 MHz, DMSO): δ 8.65 (1 H, d, J 4.1 Hz), 8.10 (1 H, s), 8.01 (2 H, t, J 4.0 Hz), 7.96 (1 H, d, J 7.7 Hz), 7.78 (1 H, s), 7.69-7.66 (3 H, m), 7.32-7.28 (1 H, m), 7.26-7.20 (1 H, m), 6.99 (1 H, t, J 9.0 Hz), 5.25 (2 H, s); *m/z* (ES^+) 405 [MH^+].

Example 16

1-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)pyridin-3-yl]ethanol

2-({4-[(2,4-Difluorophenoxy)methyl]phenyl}sulfonyl)nicotinaldehyde (Example 15, Step 1, 0.2g, 0.51 mmol) was dissolved in THF (5 mL) and methyl magnesium bromide (3 M in THF, 0.51 ml, 1.54 mmol) was added. The reaction was stirred for 1 h before being quenched with saturated ammonium chloride solution. The mixture was acidified with 10% citric acid and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography on silica, eluting with 35% ethyl acetate/isohexane, followed by recrystallisation from ethyl acetate/heptane to yield the title compound (35 mg, 17%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.39 (1 H, d, J 3.5 Hz), 8.17 (1 H, d, J 8.0 Hz), 8.03 (2 H, d, J 8.2 Hz), 7.64 (2 H, d, J 8.1 Hz), 7.46 (1 H, dd, J 4.6, 7.9 Hz), 6.95-6.87 (2 H, m), 6.78 (1 H, t, J 8.0 Hz), 5.98 (1 H, q, J 6.4 Hz), 5.19 (2 H, s), 2.85 (1 H, s), 1.63 (3 H, d, J 6.4 Hz); *m/z* (ES^+) 392 [MH^+].

Example 17

2-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)phenyl]-1,3-thiazole

Step 1: 2-bromobenzenecarbothioamide

A mixture of 2-bromobenzamide (2 g, 10 mmol) and 2,4-bis(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane-2,4-disulfide (4.5 g, 11 mmol) in tetrahydrofuran (10 mL) was heated to 80 °C for 3 h. The cooled reaction mixture was partitioned between EtOAc and water. The organic layer was washed with water and brine, dried over $MgSO_4$ and adsorbed onto silica. Purification by dry flash column chromatography on silica, eluting with 20% ethyl acetate/isohexane, gave 2-bromobenzenecarbothioamide (400 mg, 19%). ^{1}H NMR (400 MHz, DMSO): δ 10.10 (1 H, s), 9.63 (1 H, s), 7.58 (1 H, dd, J 1.0, 8.0 Hz), 7.39-7.23 (3 H, m).

Step 2: 2-(2-bromophenyl)-1,3-thiazole

2-Bromobenzenecarbothioamide (Step 1, 500 mg, 2.3 mmol) and bromoacetaldehyde diethyl acetal (0.34 mL, 2.3 mmol) were combined in ethanol (1.2 mL) and heated to 78 °C under nitrogen for 2 h. The cooled reaction mixture was partitioned between EtOAc and water. The organic layer was washed with brine, dried over $NaSO_4$ and evaporated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 15% ethyl acetate/isohexane, to give the title compound (365 mg, 66%). ^{1}H NMR (400 MHz, DMSO): δ 8.02-7.98 (2 H, m), 7.94 (1 H, d, J 3.2 Hz), 7.80 (1 H, dd, J 1.2, 8.0 Hz), 7.54-7.50 (1 H, m), 7.42-7.38 (1 H, m).

Step 3: 2-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)phenyl]-1,3-thiazole

The title compound was prepared from 2-(2-bromophenyl)-1,3-thiazole (Step 2) and sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate (Intermediate 1) according to the method of Example 15, Step 1. ^{1}H NMR (400 MHz, DMSO): δ 8.34-8.30 (1 H, m), 7.88-7.80 (4 H, m), 7.73 (2 H, d, J 8.4), 7.60-7.58 (3 H, m), 7.33-7.21 (2 H, m), 7.05-6.99 (1 H, m), 5.26 (2 H, s); *m/z* (ES^+) 444 [MH^+].

Example 18

2-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)pyridin-3-yl]propan-2-ol

Step 1: 2-(2-bromopyridin-3-yl)propan-2-ol

Lithium diisopropylamide (2 M in tetrahydrofuran, 12.5 mL, 25 mmol) was dissolved in THF (40 mL) and cooled to -78 °C. 2-Bromopyridine (3.9 g, 25 mmol) was added dropwise and the reaction was stirred for 3 h before adding acetone (1 mL, dried over freshly activated molecular sieves) and allowed to warm to room temperature. The reaction was quenched with saturated ammonium chloride and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and evaporated. The residue was purified by flash column chromatography, eluting with 20% ethyl acetate/isohexane to give the title compound a solid (1.4 g, 26%). ^{1}H NMR (500 MHz, DMSO): δ 8.22 (1 H, dd, J 1.9, 4.5 Hz), 8.18 (1 H, dd, J 1.9, 7.8 Hz), 7.43 (1 H, dd, J 4.5, 7.7 Hz), 5.42 (1 H, s), 1.62 (6 H, s).

Step 2: 2-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)pyridin-3-yl]propan-2-ol

The title compound was prepared from 2-(2-bromopyridin-3-yl)propan-2-ol (Step 1) and sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate (Intermediate 1) according to the method of Example 15, Step 1. ^{1}H NMR (500 MHz, DMSO): δ 8.34 (1 H, d, J 7.5 Hz), 8.29 (1 H, d, J 3.4 Hz), 7.88 (2 H, d, J 8.1 Hz), 7.66 (2 H, d, J 8.1 Hz), 7.56 (1 H, dd, J 4.4, 8.0 Hz), 7.32-7.24 (2 H, m), 7.01 (1 H, t, J 8.5 Hz), 5.51 (1 H, s), 5.28 (2 H, s), 1.76 (6 H, s); *m/z* (ES^+) 420 [MH^+].

Example 19

3-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)phenyl]-4*H*-1,2,4-triazole

Step 1: 2-iodo-*N*'-4*H*-1,2,4-triazol-4-ylbenzenecarboximidamide

4*H*-1,2,4-Triazol-4-amine (5.0 g, 0.06 mol) and 2-iodobenzonitrile (13.6 g, 0.06 mol) were added to sodium ethoxide (21% in ethanol, 0.06 mol) and heated to 78 °C for 5 h. The cooled reaction mixture was poured into water and the resulting precipitate filtered off and azeotroped with toluene to give the title compound as a solid (15.6 g, 81%). ^{1}H NMR (400 MHz, DMSO): δ 8.40 (2 H, s), 7.92 (1 H, d, J 7.6 Hz), 7.51-7.43 (3 H, m), 7.37 (1 H, d, J 4.3 Hz), 7.25-7.19 (1 H, m).

Step 2: 3-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)phenyl]-4*H*-1,2,4-triazole

Ethylchloroformate (3.9 mL, 0.05 mol) and 2-iodo-*N*'-4*H*-1,2,4-triazol-4-ylbenzenecarboximidamide (Step 1, 15.6 g, 0.05 mol) were combined in acetonitrile (75 mL) under nitrogen and heated to reflux overnight. The cooled reaction mixture was filtered to collect the preciptate which was azeotroped with toluene to give 3-(2-iodophenyl)-4*H*-1,2,4-triazole. The solid (6.5 g) was dissolved in THF (57 mL) and DMF (57 mL) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 2.1 g, 50.1 mmol) was added and the reaction stirred for 20 min. 2-(Trimethylsilyl)ethoxymethyl chloride (4.6 mL, 26.3 mmol) was added and the reaction stirred overnight at room temperature. The reaction was quenched with MeOH then partitioned between water and EtOAc. The organic layer was washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with 50% ethyl acetate/isohexane, then used according to the method of Example 15 Step 1, followed by SEM-deprotection using trifluoroacetic acid in dichloromethane, to give the title compound. ^{1}H NMR (400 MHz, DMSO): δ 14.13 (1 H, s), 8.56 (1 H, s), 8.26 (1 H, t, J 4.5 Hz), 7.90-7.75 (4 H, m), 7.60-7.55 (3 H, m), 7.32-7.20 (2 H, m), 7.02-6.98 (1 H, m), 5.24 (2 H, s); *m/z* (ES^+) 428 [MH^+].

Example 20

2-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)phenyl]-1*H*-imidazole

2-(2-Bromophenyl)-1*H*-imidazole (WO 9407486; 1.0 g, 4.48 mmol) was dissolved in THF (11 mL) and DMF (11 mL) and cooled to 0 °C. Sodium hydride (60% dispersion in mineral oil, 197 mg, 4.93 mmol) was added and the reaction stirred for 20 min. 2-(Trimethylsilyl)ethoxymethyl chloride (0.79 mL, 4.93 mmol) was added and the reaction stirred overnight at room temperature. The reaction was quenched with MeOH then partitioned between water and Et_2O. The organic layer was dried over $MgSO_4$ and

concentrated *in vacuo*. The residue was purified by flash column chromatography, then used according to the method of Example 15 Step 1, followed by SEM-deprotection using trifluoroacetic acid in dichloromethane, to give the title compound. ^{1}H NMR (500 MHz, DMSO): δ 12.10 (1 H, s), 8.24 (1 H, d, J 6.9 Hz), 7.77-7.71 (2 H, m), 7.65 (2 H, d, J 8.0 Hz), 7.53-7.50 (3 H, m), 7.29 (1 H, t, J 8.6 Hz), 7.23-7.18 (2 H, m), 6.99 (1 H, t, J 7.6 Hz), 6.90 (1 H, s), 5.20 (2 H, s); *m/z* (ES$^+$) 427 [MH$^+$].

Example 21

2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)-3-(1*H*-imidazol-2-yl)pyridine

Step 1: 2-bromo-3-(1*H*-imidazol-2-yl)pyridine

A mixture of 2-bromonicotinaldehyde (5.0 g, 26.9 mmol) and glyoxal (3.85 mL, 33.6 mmol) in ammonium solution (4.28 ml, 67.3 mmol) and MeOH (75 mL) was stirred for 12 h at ambient temperature. The reaction was concentrated in vacuo and the resultant residue diluted with EtOAc and water. The phases were separated; the organics washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate. The resultant solid was washed with Et_2O to yield the title product as a white solid (850 mg, 14%). ^{1}H NMR (500 MHz, DMSO): δ 12.42 (1 H, s), 8.42 (1 H, dd, J 1.9, 4.7), 8.05 (1 H, dd, J 1.9, 7.6), 7.55 (1 H, dd, J 4.6, 7.6), 7.21 (2 H, s); *m/z* (ES$^+$) 225/226 [MH$^+$].

Step 2: 2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)-3-(1*H*-imidazol-2-yl)pyridine

Sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate (Intermediate 1; 164 mg, 0.53 mmol), 2-bromo-3-(1*H*-imidazol-2-yl)pyridine (100 mg, 0.45 mmol) and copper iodide (424 mg, 2.23 mmol) were combined in DMSO (2.2 mL) and heated to 110 °C under a nitrogen atmosphere for 2.5 h. The reaction was diluted with EtOAc (10 mL) and aqueous ammonium hydroxide solution (10 mL). The phases were separated; the organics washed with 1N HCl, water and brine successively, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica, eluting with ethyl acetate, to yield a white solid (125 mg, 64%). ^{1}H NMR (500 MHz, DMSO): δ 12.29 (1 H, s), 8.64 (1 H, dd, J 1.5, 4.6), 8.14 (1 H, dd, J 1.3, 7.8), 7.93 (2 H, d, J 8.2), 7.73 (1 H, dd, J 4.6, 7.8), 7.67 (2 H, d, J 8.2), 7.34-7.24 (3 H, m), 7.10 (1 H, s), 7.05-6.99 (1 H, m), 5.29 (2 H, s); *m/z* (ES$^+$) 428 [MH$^+$].

Example 22

1-[2-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)pyridin-3-yl]cyclobutanol

The title compound was prepared from sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate (Intermediate 1) and 1-(2-bromopyridin-3-yl)cyclobutanol (prepared as described in Example 18, Step 1, using cyclobutanone in place of acetone) to give the title compound as a white solid. ^{1}H NMR (500 MHz, DMSO): δ 8.41 (1 H, dd, J 1.3, 4.5), 8.07 (1 H, dd, J 1.3, 7.9), 7.94 (2 H, d, J 8.3), 7.67 (2 H, d, J 8.2),

7.60 (1 H, dd, J 4.5, 7.9), 7.34-7.26 (2 H, m), 7.05-7.01 (1 H, m), 5.51 (1 H, s), 5.29 (2 H, s), 2.72-2.66 (2 H, m), 2.50-2.45 (2 H, m), 2.04-1.96 (1 H, m), 1.65-1.57 (1 H, m). *m/z* (ES^+) 414 [$(M-OH)^+$].

Example 23

1-[2-({4-[(4-fluorophenoxy)methyl]phenyl}sulfonyl)pyridin-3-yl]cyclobutanol

The title compound was prepared from sodium 4-[(4-fluorophenoxy)methyl]benzenesulfinate (prepared as described in Intermediate 1, Method 2, using 4-fluorophenol in Step 1) and 1-(2-bromopyridin-3-yl)cyclobutanol (prepared as described in Example 22), to give the title compound as a white solid. ^1H NMR (500 MHz, DMSO): δ 8.41 (1 H, dd, J 1.3, 4.5), 8.07 (1 H, dd, J 1.3, 8.0), 7.92 (2 H, d, J 7.6), 7.67 (2 H, d, J 8.2), 7.60 (1 H, dd, J 4.5, 7.9), 7.16-7.12 (2 H, m), 7.07-7.03 (2 H, m), 5.50 (1 H, s), 5.22 (2 H, s), 2.72-2.66 (2 H, m), 2.48 (2 H, m), 2.01 (1 H, m), 1.65-1.57 (1 H, m); *m/z* (ES^+) 396 [$(M-OH)^+$].

Example 24

4-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)-1*H*-benzimidazole

Step 1: 1,2-Diamino-3-bromobenzene

To a stirring slurry of tin(II) chloride dihyrate (11.8 g, 52.3 mmol) in conc. hydrochloric acid (55 mL) was added 2-bromo-6-nitroaniline (2.84 g, 13.1 mmol), and the resulting mixture was stirred at room temperature for 5 minutes – an exotherm was observed. The mixture was then stirred at reflux for 30 minutes. After cooling to room temperature, the slurry was poured onto crushed ice (200 mL), and the pH was adjusted to 14 by the addition of sodium hydroxide pellets. The resulting mixture was washed with diethyl ether (5 x 100 mL), then the combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by chromatography on a Biotage SP1 apparatus, on a 40S silica gel column, eluting with 5% to 50% ethyl acetate in dichloromethane, yielding the product as a yellow-brown oil, which solidified upon standing (2.02 g, 87%). ^1H NMR (400 MHz, $CDCl_3$): δ 6.97 (1 H, dd, J 1.4, 8.0 Hz), 6.64 (1 H, dd, J 1.4, 7.8 Hz), 6.56 (1 H, t, J 7.9 Hz), 3.61 (3 H, s); *m/z* (ES^+) 187/189 [MH^+].

Step 2: 4-Bromo-1*H*-benzimidazole

A solution of 1,2-diamino-3-bromobenzene (2.00 g, 10.7 mmol) in formic acid (10 mL) was stirred at 100°C for 1 hour. The pH of the mixture was adjusted to 14 by the addition of 4M sodium hydroxide solution, precipitating the product as a solid. This was separated by filtration, washed with water and air-dried affording the product as an off-white solid. A further crop of equally pure material precipitated from the filtrate upon standing at room temperature for a few days. Total yield = 1.98 g, 94%. ^1H NMR (500 MHz, DMSO): δ 12.83 (1 H, s), 8.30 (1 H, s), 7.58 (1 H, d, J 7.9 Hz), 7.41 (1 H, d, J 7.1 Hz), 7.14 (1 H, t, J 7.8 Hz); *m/z* (ES^+) 197, 199 [MH^+].

Step 3: 4-Iodo-1*H*-benzimidazole

Two reactions were set up as follows: A mixture of 4-bromo-1*H*-benzimidazole (725 mg, 3.68 mmol),

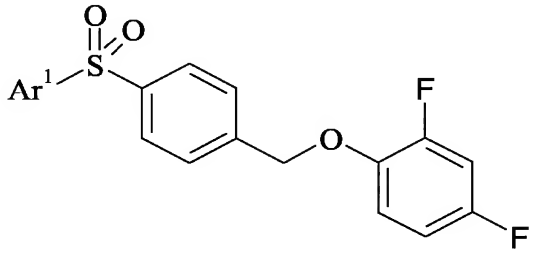
sodium iodide dihydrate (1.37 g, 7.36 mmol), copper(I) iodide (70 mg, 0.37 mmol) and *N,N'*-dimethylethylenediamine (78 μL, 65 mg, 0.74 mmol) in dioxane (8 mL) was irradiated at 150°C in a microwave reactor for 2.5 h. The two reaction mixtures were combined, diluted with water (90 mL) and conc. ammonia (20 mL), then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with water (20 mL), then with saturated sodium chloride solution (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash chromatography on silica gel, eluting with ethyl acetate, yielding the product as a yellow-white solid (1.40 g, 78%). ^{1}H NMR (400 MHz, DMSO): δ 12.72 (1 H, s), 8.28 (1 H, s), 7.61-7.53 (2 H, m), 7.01 (1 H, t, J 7.8 Hz); *m/z* (ES^+) 245 [MH^+].

Step 4: 4-({4-[(2,4-difluorophenoxy)methyl]phenyl}sulfonyl)-1*H*-benzimidazole

The title compound was prepared from sodium 4-[(2,4-difluorophenoxy)methyl]benzenesulfinate (Intermediate 1, Method 2, Step 4) and 4-iodo-1*H*-benzimidazole to give the title compound as a white solid. ^{1}H NMR (500 MHz, DMSO): δ 12.95 (1 H, s), 8.38 (1 H, s), 8.17 (2 H, d, J 8.2), 7.94 (1 H, d, J 7.9), 7.86 (1 H, d, J 7.6), 7.63 (2 H, d, J 8.2), 7.42 (1 H, t, J 7.9), 7.31-7.19 (2 H, m), 6.98 (1 H, t, J 8.8), 5.22 (2 H, s); *m/z* (ES^+) 401 [MH^+].

Examples 25-31

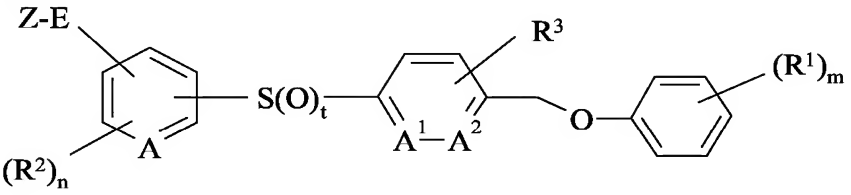
Using analogous procedures, the following were also prepared as described in Example 21 (Step 2):



Example	Ar^1	*m/z* (ES^+) [MH^+]
25	Methyl 2-benzoate	419
26	2-[1-pyridin-3-ylmethanol]	392
27	2-[(1*S*)-1-phenylethanol]	405
28	2-[(1*R*)-1-pyridin-3-ylethanol]	406
29	2-[(1*S*)-1-pyridin-3-ylethanol]	406
30	2-(4*H*-pyrazol-3-yl)benzene	427
31	2-benzenesulfonamide	439

CLAIMS

1. A pharmaceutical composition comprising, in a pharmaceutically acceptable carrier, a compound of formula I:



I

or a pharmaceutically acceptable salt thereof; wherein

m is 0, 1, 2 or 3;

n is 0, 1 or 2;

t is 1 or 2;

A represents CH or N;

A^1 and A^2 each represent CH or N but do not both represent N:

E represents a chemical bond or a straight or branched alkylene chain containing from 1 to 4 carbon atoms, optionally incorporating an oxygen atom to form an ether linkage;

Z is selected from halogen, CN, nitro, CF_3, OCF_3, $-R^a$, $-OR^a$, $-SR^a$, $-SOR^a$, $-SO_2R^a$, $-SO_2NR^aR^b$, $-NR^aR^b$, $-NR^aCOR^b$, $-NR^aCO_2R^b$, $-NR^aCO_2NR^aR^b$, $-NR^aS(O)_tR^a$, $-NR^aSO_2NR^aR^b$, $-COR^a$, $-CO_2R^a$, $-CONR^aR^b$, $-CR^a{=}NOR^b$ or a five- or six-membered heteroaromatic ring optionally bearing up to 2 substituents selected from halogen, CN, CF_3, C_{1-6}alkyl, C_{1-6}alkoxy, C_{1-6}alkylthio, amino, C_{1-6}alkylamino and di(C_{1-6})alkylamino;

or the moiety –E-Z may combine with an adjacent R^2 group as defined below;

R^a and R^b independently represent H or a hydrocarbon group of up to 7 carbon atoms which is optionally substituted with up to 3 fluorine atoms and optionally with Cl, Br, CN, OH, C_{1-4}alkoxy, C_{1-4}alkylthio, amino, C_{1-4}alkylamino or di(C_{1-4})alkylamino; or R^a and R^b, when linked through a nitrogen atom, together represent the residue of a heterocyclic ring of 4, 5 or 6 members, optionally bearing up to 3 substituents selected from halogen, CN, CF_3, oxo, OH, C_{1-4}alkyl and C_{1-4}alkoxy;

each R^1 independently represents halogen, CN, OH, C_{1-4} alkoxy or hydroxymethyl;

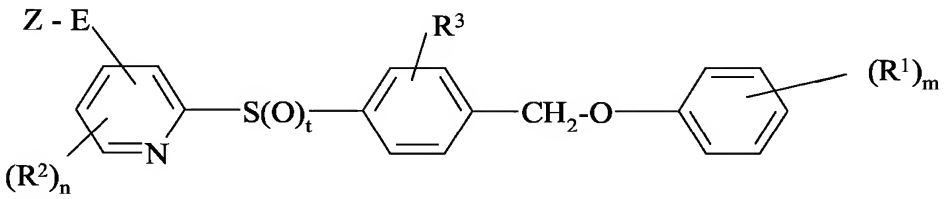
each R^2 independently represents halogen, CN, $CONH_2$, C_{1-4}alkyl or C_{1-4}alkoxy; or an R^2 group and the moiety –E-Z when attached to adjacent ring positions may complete a fused imidazole ring;

and R^3 represents H, halogen, CN, CF_3, OR^a, CO_2R^a, $CONR^aR^b$, NR^aR^b or C_{1-4}alkyl which is optionally substituted with halogen, CN, CF_3, OR^a, CO_2R^a, $CONR^aR^b$ or NR^aR^b.

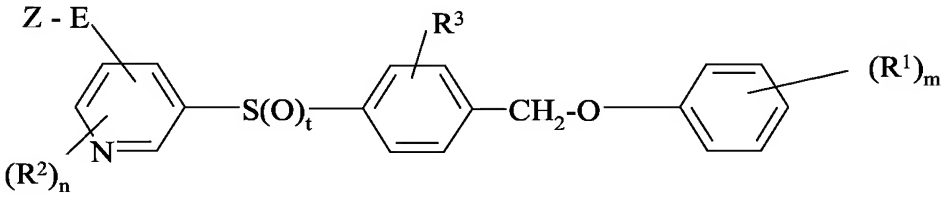
2. A compound according to formula I as defined in claim 1, or a pharmaceutically acceptable salt thereof, wherein –E-Z is other than H.

3. A compound according to claim 2 in which m is 1 or 2 and R^1 represents fluorine.

4. A compound according to claim 2 or claim which is a compound of formula II or formula III:



II,

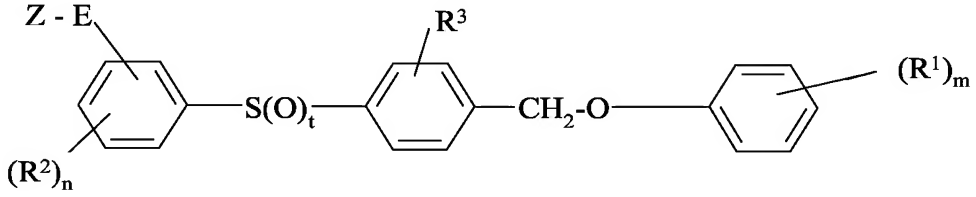


III

or a pharmaceutically acceptable salt thereof.

5. A compound according to claim 4 wherein the moiety –E-Z is attached at a ring position adjacent to the point of attachment of the $-S(O)_t-$ moiety

6. A compound corresponding to claim 2 or claim 3 which is a compound of formula IV:



IV

or a pharmaceutically acceptable salt thereof.

7. A compound according to any of claims 2-6 wherein the moiety –E-Z is selected from: halogen, hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxypropyl, 1-hydroxy-1-methylethyl, 1-hydroxycyclobutyl, CO_2Me, CO_2Et, $CONH_2$, CONHMe, $COCH_3$, NH_2, NHMe, NMe_2, $NHSO_2Me$, SO_2Me, CN, SO_2NH_2, pyrazol-3-yl, imidazol-2-yl and thiazol-3-yl.

8. A compound according to any of claims 2-7 for use in medicine.

9. The use of a compound of formula I as defined in claim 1 for the manufacture of a medicament for treating or preventing a condition mediated by 5-HT_{2A} receptor activity.

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/050048

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/10 A61K31/44 C07C317/14 C07D213/71 A61P25/00
A61K31/166 A61K31/18 A61K31/277 A61K31/415 A61K31/4164
A61K31/4184 A61K31/4196 A61K31/426 C07D213/80 C07D213/82

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/086661 A (AMGEN INC; AKERMAN, MICHELLE; HOUZE, JONATHAN; LIN, DANIEL, C., H; LIU) 22 September 2005 (2005-09-22) abstract; claims 1-52	1,2,4,6, 8
A	FLETCHER S R ET AL: "4-(Phenylsulfonyl)piperidines: Novel, Selective, and Bioavailable 5-HT2A Receptor antagonists" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 45, no. 2, 2002, pages 492-503, XP002290071 ISSN: 0022-2623 cited in the application the whole document	1-9

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

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"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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Date of the actual completion of the international search	Date of mailing of the international search report
3 August 2006	22/08/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Golebiowska, K

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/050048

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	SCHOP H ET AL: "Partial resistance of E. coli mutants against 2,4-diamino-5-benzylpyrimidines by interactions with bacterial membrane lipopolysaccharides. Derivation of quantitative structure-binding relationships" EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, EDITIONS SCIENTIFIQUE ELSEVIER, PARIS, FR, vol. 35, no. 6, June 2000 (2000-06), pages 619-634, XP004330453 ISSN: 0223-5234 Table II, Entry 2 - K-96 abstract	1-9
A	COLEMAN, MICHAEL D. ET AL: "Preliminary evaluation of the toxicity and efficacy of novel 2,4-diamino-5-benzylpyrimidine-sulfone derivatives using rat and human tissues in vitro" ENVIRONMENTAL TOXICOLOGY AND PHARMACOLOGY , 2(4), 389-395 CODEN: ETOPFR; ISSN: 1382-6689, 1996, XP002393315 Figure I, K-120 abstract	1-9
A	MARTYN D WOOD, DAVID R THOMAS, JEANNETTE M WATSON,: "Therapeutic potential of serotonin antagonists in depressive disorders" EXPERT OPINION ON INVESTIGATIONAL DRUGS, vol. 11, no. 4, April 2002 (2002-04), pages 457-467, XP002393316 ISSN: 1357-3784 abstract page 457, paragraph 1 - page 458, column 2, paragraph 3 page 460, column 2, paragraphs 2,3	1-9

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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2006/050048

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HOWARD H.R.: "ANTIPSYCHOTIC DRUGS: RECENT DEVELOPMENTS AND NOVEL AGENTS" EXPERT OPINION ON THERAPEUTIC PATENTS, vol. 7, no. 4, April 1997 (1997-04), pages 353-369, XP002393317 ISSN: 1354-3776 abstract page 353, column 1, paragraph 1 - page 354, column 2, paragraph 3 page 363, column 2, paragraph 2; compounds 90-94	1-9
A	DATABASE REGISTRY [Online] Chemical Abstract Service, COPYRIGHT (C) 2006 American Chemical Society (ACS); See CAS RN 695157-04-1 18 June 2004 (2004-06-18), XP002393322 retrieved from STN abstract	1-9
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A	DATABASE REGISTRY [Online] Chemical Abstract Service, COPYRIGHT (C) 2006 American Chemical Society (ACS); See CAS RN 695155-15-8 18 June 2004 (2004-06-18), XP002393324 retrieved from STN abstract	1-9

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2006/050048

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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